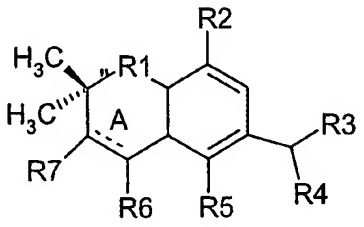
We claim:

1. A pharmaceutical composition comprising a compound of formula (I)



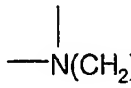
wherein

A is a π bond or absent;

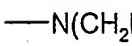
R1 is O, S, or F;

R2 is H, OH, branched or unbranched C_{1-12} alkyl, alkoxy, aryl, heterocycle, imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, or acyl;

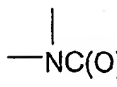
R3 is H, OH, branched or unbranched C_{1-12} alkyl, alkoxy, aryl, heterocycle, imidazole, substituted imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, acyl , or Z, wherein Z is NH_2,



$$—N(CH_2)_2NH_2,$$

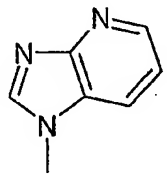


$$—N(CH_2NH_2)C(O)CH_3,$$

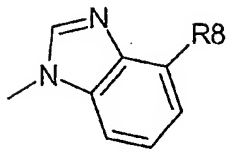


$$—NC(O)CH_2NH_2,$$

—N(C(O)NH_2)CH_2CH_3,



or



wherein R8 is H,OH, alkyl, alkoxy, or halo;

R4, R6 and R7 are independently H, OH, branched or unbranched C_{1-12} alkyl, alkenyl, alkoxy, aryl, heterocycle, imidazole, substituted imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, or acyl;

R5 is H, OH, halo, alkyl, or alkoxy; or

a pharmaceutically acceptable salt or prodrug thereof in an amount sufficient to inhibit intracellular HIF-1 activity.

2. A pharmaceutical composition comprising one more compounds selected from the group consisting of

1-[(2,2-dimethyl-2*H*-chromen-6-yl)(phenyl)methyl]-1*H*-imidazole;

1-[(2,2-dimethyl-4a,8a-dihydro-2*H*-chromen-6-yl)(4-methylphenyl)methyl]-1*H*-imidazole;

1-[(2,2-dimethyl-2*H*-chromen-6-yl)(3-methoxyphenyl)methyl]-1*H*-imidazole;

1-[(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)(4-methylphenyl)methyl]-1*H*-imidazole;

1-[(2,2-dimethyl-2*H*-chromen-6-yl)(4-fluoro-3-methylphenyl)methyl]-1*H*-imidazole;

1-[(4-chlorophenyl)(2,2-dimethyl-2*H*-chromen-6-yl)methyl]-1*H*-imidazole;

1-[(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)(phenyl)methyl]-1*H*-imidazole;

1-[1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-methylbutyl]-1*H*-imidazole;

1-[(3,3-dimethyl-7,10-dihydro-3*H*-benzo[*f*]chromen-8-yl)(4-fluoro-3-methylphenyl)methyl]-1*H*-imidazole;

1-[(3,3-dimethyl-7,10-dihydro-3*H*-benzo[*f*]chromen-8-yl)(3-methoxyphenyl)methyl]-1*H*-imidazole;

1-[(3,3-dimethyl-7,10-dihydro-3*H*-benzo[*f*]chromen-8-yl)(4-methylphenyl)methyl]-1*H*-imidazole;

1-[(8-methoxy-2,2-dimethyl-2*H*-chromen-7-yl)(phenyl)methyl]-1*H*-imidazo[4,5-*b*]pyridine;

1-[1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethyl]-1*H*-imidazo[4,5-*b*]pyridine;

1-[1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-methylbutyl]-1*H*-imidazo[4,5-*b*]pyridine;

1-[1-(3,3-dimethyl-7,10-dihydro-3*H*-benzo[*f*]chromen-8-yl)-3-methylbutyl]-1*H*-imidazo[4,5-*b*]pyridine;

4-chloro-1-[cyclohexyl(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)methyl]-1*H*-benzimidazole;

1-[cyclohexyl(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)methyl]-1*H*-benzimidazole;

1-[1-(2,2-dimethyl-2*H*-chromen-6-yl)prop-2-en-1-yl]-2-methyl-1*H*-benzimidazole;

1-[cyclohexyl(2,2,6-trimethyl-2*H*-chromen-8-yl)methyl]-1*H*-benzimidazole;

(2,2-dimethyl-2*H*-chromen-6-yl)(3-hydroxyphenyl)methyl biphenyl-4-carboxylate;

N-isopropyl-3,4-dimethoxy-*N*-[(8-methoxy-2,2-dimethyl-2*H*-chromen-7-yl)methyl]benzenesulfonamide;

1-[(4-tert-butylphenyl)(2,2-dimethyl-4a,8a-dihydro-2H-chromen-6-yl)methyl]-1H-imidazole;

N-[(2,2-dimethyl-4a,8a-dihydro-2*H*-chromen-6-yl)(phenyl)methyl]-*N*-ethylurea;

N-[(2,2-dimethyl-4a,8a-dihydro-2*H*-chromen-6-yl)(phenyl)methyl]-*N*-methylethane-1,2-diamine;

N-(aminomethyl)-*N*-[(2,2-dimethyl-4a,8a-dihydro-2*H*-chromen-6-yl)(phenyl)methyl]acetamide; and

N^1-[(2,2-dimethyl-4a,8a-dihydro-2*H*-chromen-6-yl)(phenyl)methyl]-N^1-methylglycinamide

in an amount effective to modulate intracellular HIF-1 activity.

3. A pharmaceutical composition comprising a hydrolysis, oxidation, or reduction reaction product of any of the compounds of claims 1 and 2.

4. The pharmaceutical composition of claim 3, wherein the hydrolysis, oxidation, or reduction reaction opens a nitrogen containing ring of any of the compounds of claims 1-2.

5. The pharmaceutical composition of claims 1-4, further comprising a second therapeutic agent.

6. The pharmaceutical composition of claim 5, wherein the second therapeutic agent is an antibiotic, anti-inflammatory, anti-oxidant, analgesic, radioisotope, nascopine, paclitaxel, nocodazole, vinca alkaloids, adriamycin, alkeran, Ara-C, BiCNU, busulfan, CCNU, carboplatinum, cisplatinum, cytoxan, daunorubicin, DTIC, 5-FU, fludarabine, hydrea, idarubicin, ifosfamide, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen, mustard, velban, vincristine, VP-16, gemcitabine, herceptin, irinotecan, camptosar, CPT-11, leustatin, navelbine, rituxan, STI-571, taxotere, topotecan, hycamtin, xeloda capecitabine, zevelin, and combinations thereof.

7. A method for the treatment or prevention of a hypoxia-related pathology comprising:

administering to a host in need of such treatment an HIF-1 inhibiting amount of any of the compositions of claims 1-6.

8. A method of modulating HIF-1 activity in a cell comprising: contacting the cell with an HIF-1 inhibiting amount of any of the compositions of claims 1-6.

9. A method of treating or preventing cancer or a tumor in a host comprising administering to the host a HIF-1 inhibiting amount of any of the compositions of claims 1-6.

10. The method of claim 9, wherein the cancer or tumor is selected from the group consisting of bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head & neck cancer, leukemia, lung cancer, lymphoma, melanoma, non-small-cell lung cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, cervical cancer, thyroid cancer, gastric cancer, brain stem glioma, cerebellar astrocytoma, cerebral astrocytoma, ependymoma, Ewing's sarcoma family of tumors,

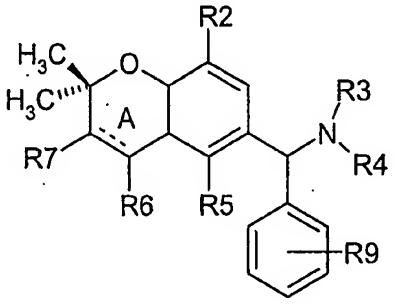
germ cell tumor, extracranial cancer, Hodgkin's disease, leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, liver cancer, medulloblastoma, neuroblastoma, brain tumors generally, non-Hodgkin's lymphoma, osteosarcoma, malignant fibrous histiocytoma of bone, retinoblastoma, rhabdomyosarcoma, soft tissue sarcomas generally, supratentorial primitive neuroectodermal and pineal tumors, visual pathway and hypothalamic glioma, Wilms' tumor, acute lymphocytic leukemia, adult acute myeloid leukemia, adult non-Hodgkin's lymphoma, chronic lymphocytic leukemia, chronic myeloid leukemia, esophageal cancer, hairy cell leukemia, kidney cancer, multiple myeloma, oral cancer, pancreatic cancer, primary central nervous system lymphoma, skin cancer, and small-cell lung cancer.

11. A method of modulating gene transcription in a cell comprising contacting the cell with an HIF-1 inhibiting amount of one or more of the compositions of any of claims 1-6.

12. The method of claim 11, wherein the cell is a cancer cell.

13. The method of claim 11, wherein the gene is VEGF, erythropoietin, glucose transporter-1, glycolytic enzymes, or tyrosine hydroxylase.

14. A pharmaceutical composition comprising a compound of formula (II):

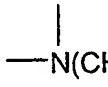


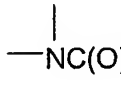
wherein

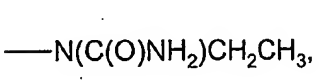
A is a π bond or absent;

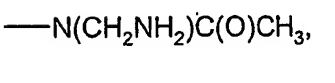
R2 is H, OH, branched or unbranched C_{1-12} alkyl, alkoxy, aryl, heterocycle, imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, or acyl;

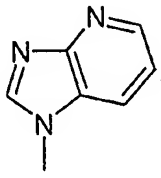
R3 is H, OH, branched or unbranched C_{1-12} alkyl, alkoxy, aryl, heterocycle, imidazole, substituted imidazole, alkyl or alkoxy substituted aryl, halo substituted aryl, halo, amine, acyl , or Z, wherein Z is NH_2,



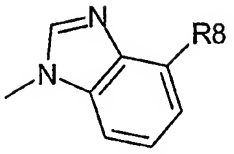








or



wherein R8 is H, OH, alkyl, alkoxy, or halo;

R4, R6, and R7 are independently H, OH, branched or unbranched C_{1-12} alkyl, alkenyl, alkoxy, aryl, heterocycle, imidazole, substituted imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, acyl;

R5 is H, OH, halo, alkyl, or alkoxy;

R9 is H, OH, halo, alkoxy, alkyl, or aryl; or

a pharmaceutically acceptable salt or prodrug thereof in an amount effective to inhibit HIF-1 intracellular activity.

15. A pharmaceutical composition comprising a hydrolysis, oxidation, or reduction reaction product of the compound of claim 14.

16. The pharmaceutical composition of claim 15, wherein the hydrolysis, oxidation, or reduction reaction opens a nitrogen containing.

17. The pharmaceutical composition of claims 13-16, further comprising a second therapeutic agent.

18. The pharmaceutical composition of claim 17, wherein the second therapeutic agent is an antibiotic, anti-inflammatory, anti-oxidant, analgesic, radioisotope, nascopine, paclitaxel, nocodazole, vinca alkaloids, adriamycin, alkeran, Ara-C, BiCNU, busulfan, CCNU, carboplatinum, cisplatinum, cytoxan, daunorubicin, DTIC, 5-FU, fludarabine, hydrea, idarubicin, ifosfamide,

methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen, mustard, velban, vincristine, VP-16, gemcitabine, herceptin, irinotecan, camptosar, CPT-11, leustatin, navelbine, rituxan, STI-571, taxotere, topotecan, hycamtin, xeloda capecitabine, zevelin, and combinations thereof.

19. A method for the treatment or prevention of a hypoxia-related pathology comprising:

administering to a host in need of such treatment an HIF-1 inhibiting amount of any of the compositions of claims 14-18.

20. A method of modulating HIF-1 activity in a cell comprising: contacting the cell with an HIF-1 inhibiting amount of any of the compositions of claims 14-18.

21. A method of treating or preventing cancer or a tumor in a host comprising administering to the host a HIF-1 inhibiting amount of any of the compositions of claims 14-18.

22. The method of claim 21, wherein the cancer or tumor is selected from the group consisting of bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head & neck cancer, leukemia, lung cancer, lymphoma, melanoma, non-small-cell lung cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, cervical cancer, thyroid cancer, gastric cancer, brain stem glioma, cerebellar astrocytoma, cerebral astrocytoma, ependymoma, Ewing's sarcoma family of tumors, germ cell tumor, extracranial cancer, Hodgkin's disease, leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, liver cancer, medulloblastoma, neuroblastoma, brain tumors generally, non-Hodgkin's lymphoma, osteosarcoma, malignant fibrous histiocytoma of bone, retinoblastoma, rhabdomyosarcoma, soft tissue sarcomas generally, supratentorial primitive neuroectodermal and pineal tumors, visual pathway

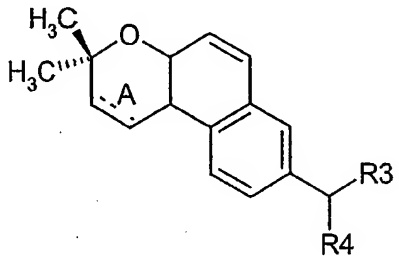
and hypothalamic glioma, Wilms' tumor, acute lymphocytic leukemia, adult acute myeloid leukemia, adult non-Hodgkin's lymphoma, chronic lymphocytic leukemia, chronic myeloid leukemia, esophageal cancer, hairy cell leukemia, kidney cancer, multiple myeloma, oral cancer, pancreatic cancer, primary central nervous system lymphoma, skin cancer, and small-cell lung cancer.

23. A method of modulating gene transcription in a cell comprising contacting the cell with an HIF-1 inhibiting amount of one or more of the compositions of any of claims 14-18.

24. The method of claim 23, wherein the cell is a cancer cell.

25. The method of claim 23, wherein the gene is VEGF, erythropoietin, glucose transporter-1, glycolytic enzymes, or tyrosine hydroxylase.

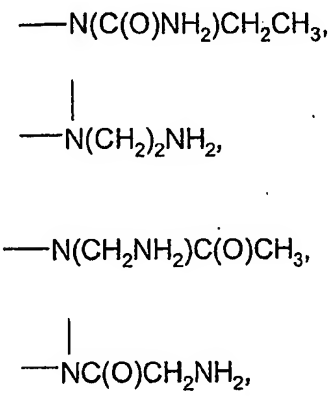
26. A pharmaceutical composition comprising a compound of formula (III):



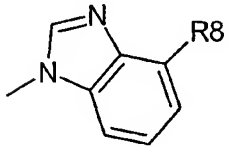
wherein

A is a π bond or absent;

R3 is H, OH, branched or unbranched C_{1-12} alkyl, alkoxy, aryl, heterocycle, imidazole, substituted imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, acyl , or Z, wherein Z is NH_2,



or



wherein R8 is H,OH, alkyl, alkoxy, or halo;

R4 is H, OH, branched or unbranched C_{1-12} alkyl, alkenyl, alkoxy, aryl, heterocycle, imidazole, substituted imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, acyl; or

a pharmaceutically acceptable salt or prodrug thereof, in an amount effective to inhibit intracellular HIF-1 activity.

27. A pharmaceutical composition comprising a hydrolysis, oxidation, or reduction reaction product of the compound of claim 26.

28. The pharmaceutical composition of claim 27, wherein the hydrolysis, oxidation, or reduction reaction opens a nitrogen containing.

29. The pharmaceutical composition of claims 26-28, further comprising a second therapeutic agent.

30. The pharmaceutical composition of claim 29, wherein the second therapeutic agent is an antibiotic, anti-inflammatory, anti-oxidant, analgesic, radioisotope, nascopine, paclitaxel, nocodazole, vinca alkaloids, adriamycin, alkeran, Ara-C, BiCNU, busulfan, CCNU, carboplatinum, cisplatinum, cytoxan, daunorubicin, DTIC, 5-FU, fludarabine, hydrea, idarubicin, ifosfamide, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen, mustard, velban, vincristine, VP-16, gemcitabine, herceptin, irinotecan, camptosar, CPT-11, leustatin, navelbine, rituxan, STI-571, taxotere, topotecan, hycamtin, xeloda capecitabine, zevelin, and combinations thereof.

31. A method for the treatment or prevention of a hypoxia-related pathology comprising:

administering to a host in need of such treatment an HIF-1 inhibiting amount of any of the compositions of claims 26-30.

32. A method of modulating HIF-1 activity in a cell comprising: contacting the cell with an HIF-1 inhibiting amount of any of the compositions of claims 26-30.

33. A method of treating or preventing cancer or a tumor in a host comprising administering to the host a HIF-1 inhibiting amount of any of the compositions of claims 26-30.

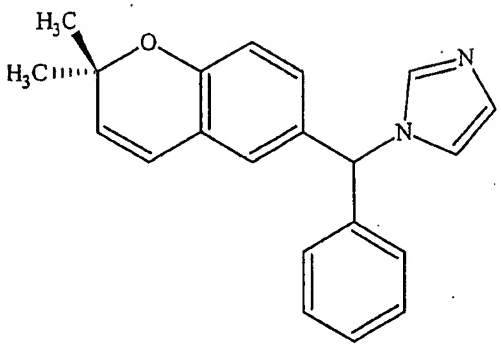
34. The method of claim 33, wherein the cancer or tumor is selected from the group consisting of bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head & neck cancer, leukemia, lung cancer, lymphoma, melanoma, non-small-cell lung cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, cervical cancer, thyroid cancer, gastric cancer, brain stem glioma, cerebellar astrocytoma, cerebral astrocytoma, ependymoma, Ewing's sarcoma family of tumors, germ cell tumor, extracranial cancer, Hodgkin's disease, leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, liver cancer, medulloblastoma, neuroblastoma, brain tumors generally, non-Hodgkin's lymphoma, osteosarcoma, malignant fibrous histiocytoma of bone, retinoblastoma, rhabdomyosarcoma, soft tissue sarcomas generally, supratentorial primitive neuroectodermal and pineal tumors, visual pathway and hypothalamic glioma, Wilms' tumor, acute lymphocytic leukemia, adult acute myeloid leukemia, adult non-Hodgkin's lymphoma, chronic lymphocytic leukemia, chronic myeloid leukemia, esophageal cancer, hairy cell leukemia, kidney cancer, multiple myeloma, oral cancer, pancreatic cancer, primary central nervous system lymphoma, skin cancer, and small-cell lung cancer.

35. A method of modulating gene transcription in a cell comprising contacting the cell with an HIF-1 inhibiting amount of one or more of the compositions of any of claims 26-30.

36. The method of claim 35, wherein the cell is a cancer cell.

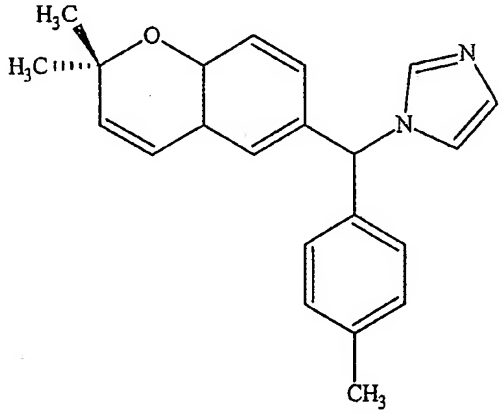
37. The method of claim 35, wherein the gene is VEGF, erythropoietin, glucose transporter-1, glycolytic enzymes, or tyrosine hydroxylase.

38. A compound of the formula:



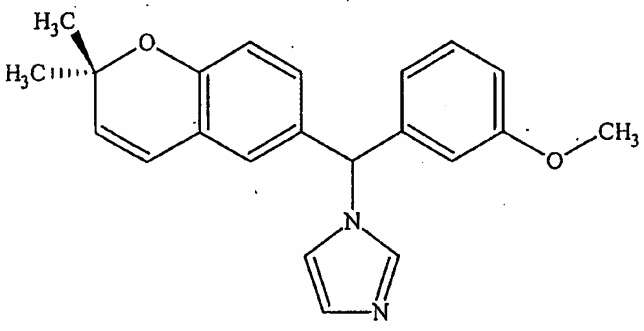
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

39. A compound of the formula:



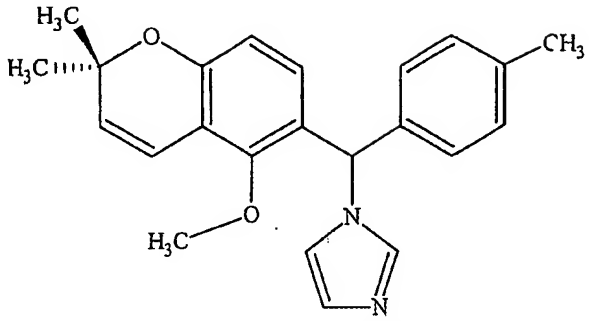
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

40. A compound of the formula:



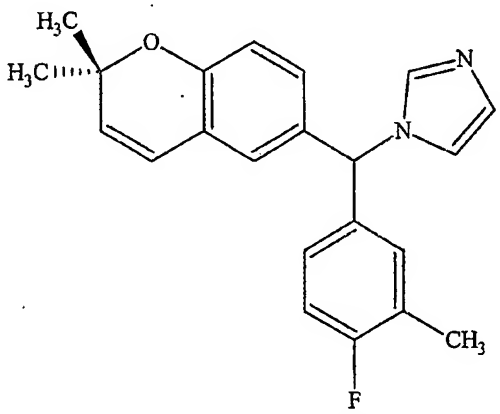
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

41. A compound of the formula:



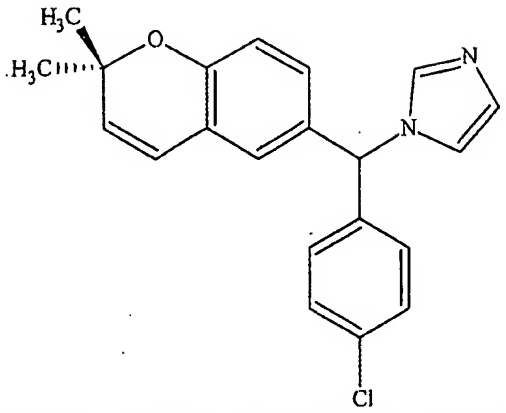
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

42. A compound of the formula:



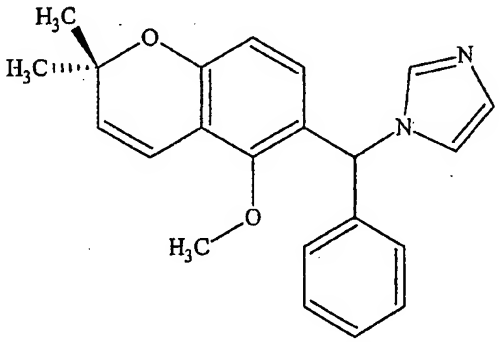
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

43. A compound of the formula:



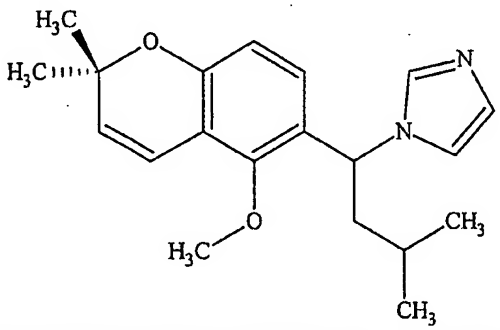
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

44. A compound of formula:



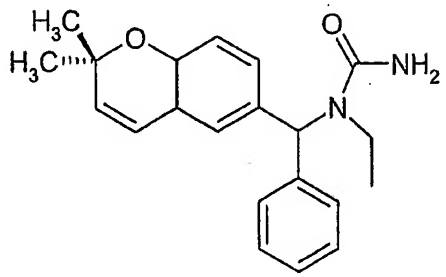
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

45. A compound of the formula:



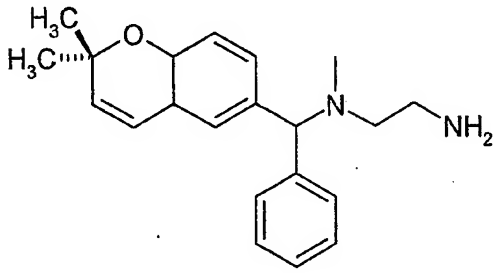
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

47. A compound of the formula:



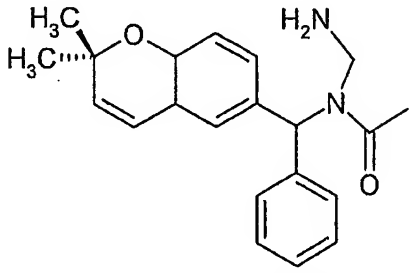
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

48. A compound of the formula:



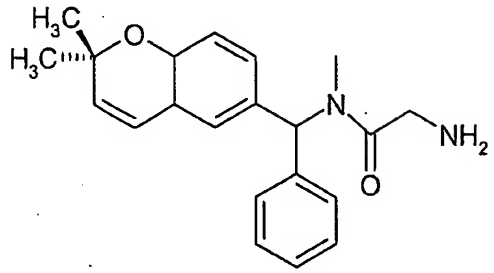
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

49. A compound of the formula:



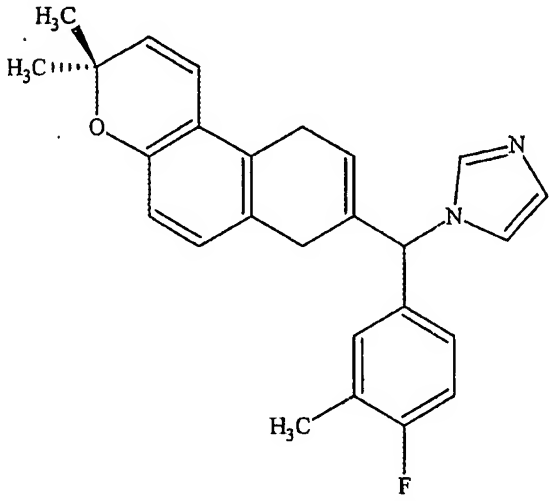
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

50. A compound of the formula:



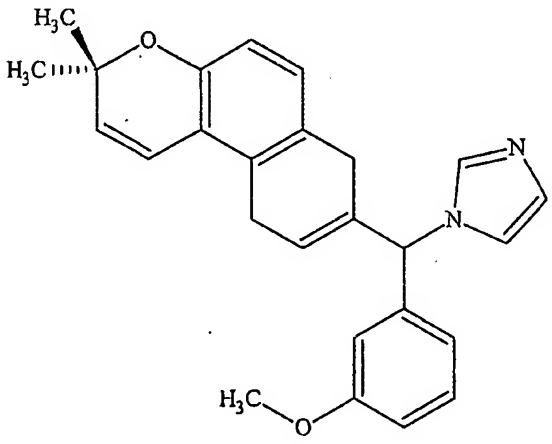
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

51. A compound of the formula:



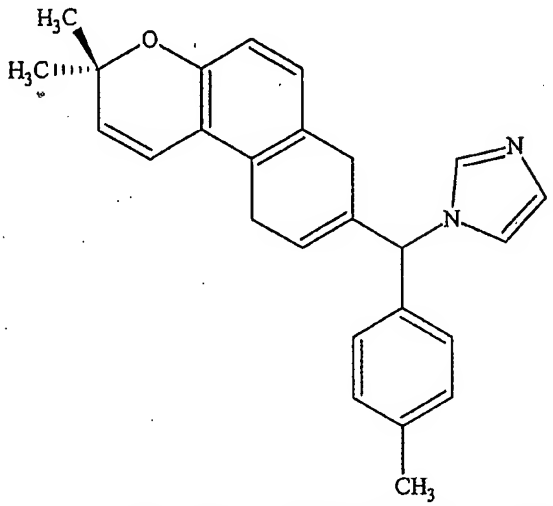
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

52. A compound of the formula:



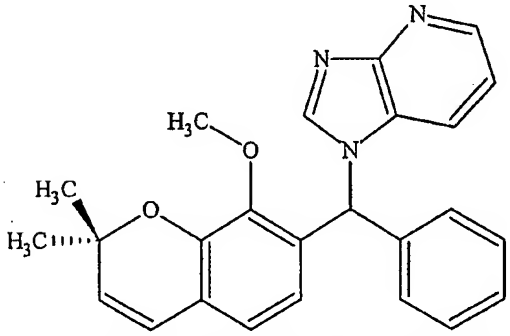
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

53. A compound of the formula:



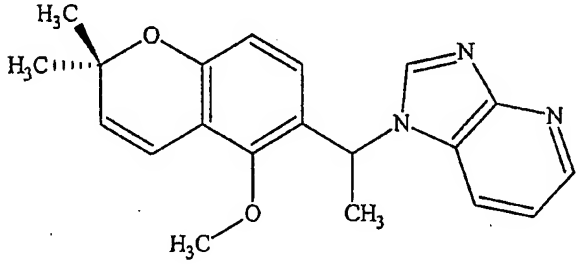
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

54. A compound of the formula:



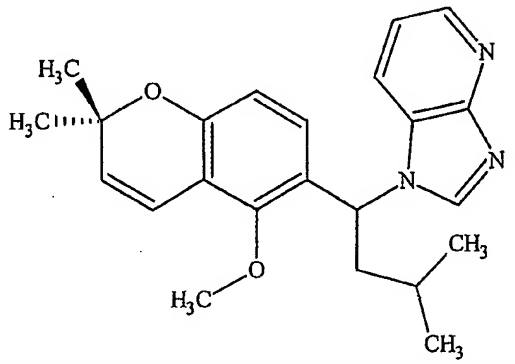
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

55. A compound of the formula:



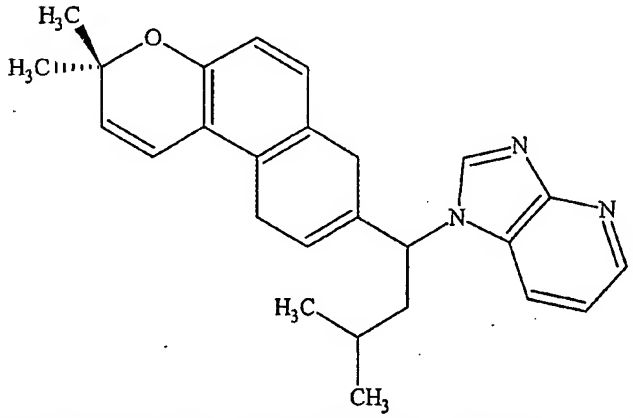
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

56. A compound of the formula:



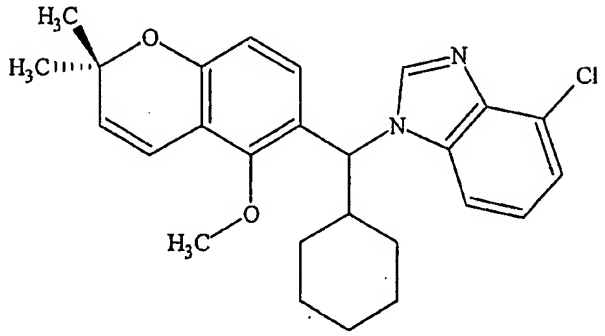
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

57. A compound of the formula:



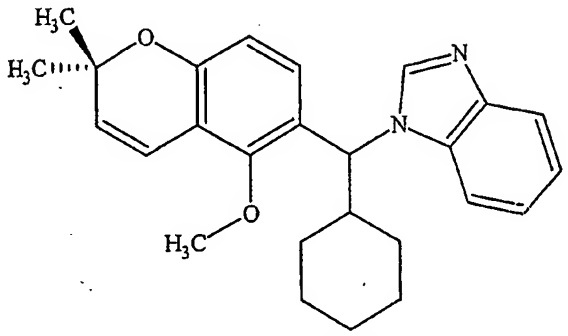
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

58. A compound of the formula:



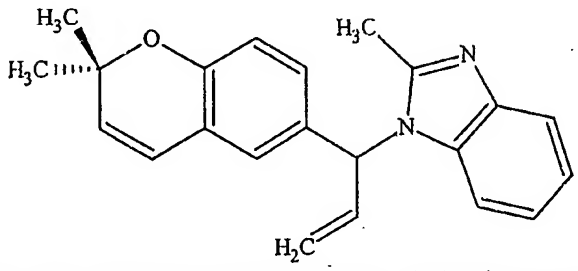
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

59. A compound of the formula:



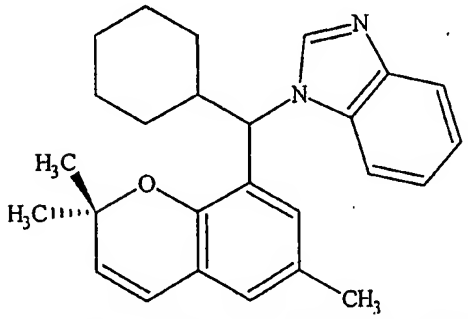
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

60. A compound of the formula:



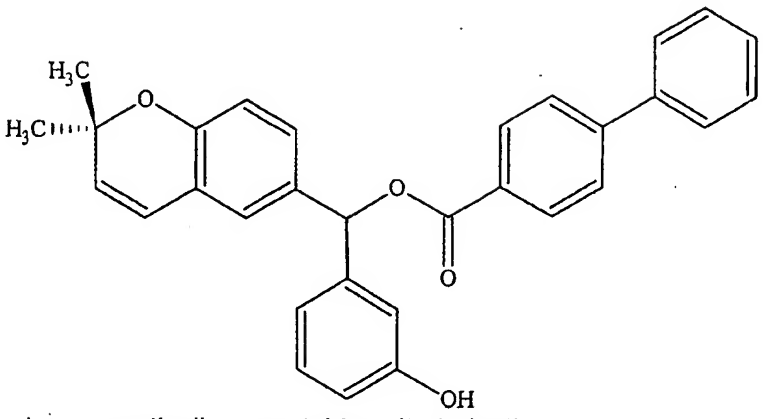
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

61. A compound of the formula:



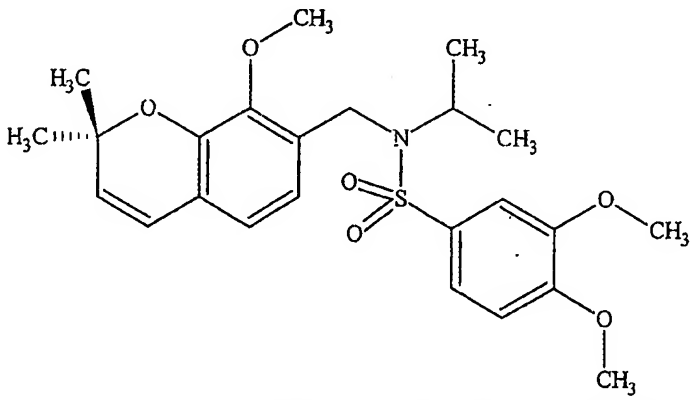
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

62. A compound of the formula:



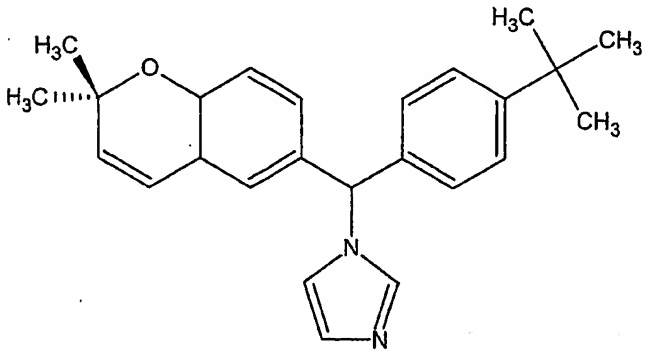
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

63. A compound of the formula:



or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

64. A compound of the formula:



or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

65. A pharmaceutical composition comprising a compound of any of claims 38-64 or a combination thereof.

66. A pharmaceutical composition comprising a hydrolysis, oxidation, or reduction reaction product of the compound of claims 38-64.

67. The pharmaceutical composition of claim 66, wherein the hydrolysis, oxidation, or reduction reaction opens a nitrogen containing.

68. The pharmaceutical composition of claim 65, further comprising a second therapeutic agent.

69. The pharmaceutical composition of claim 68, wherein the second therapeutic agent is an antibiotic, anti-inflammatory, anti-oxidant, analgesic, radioisotope, nascopine, paclitaxel, nocodazole, vinca alkaloids, adriamycin, alkeran, Ara-C, BiCNU, busulfan, CCNU, carboplatinum, cisplatinum, cytoxan, daunorubicin, DTIC, 5-FU, fludarabine, hydrea, idarubicin, ifosfamide, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen, mustard, velban, vincristine, VP-16, gemcitabine, herceptin, irinotecan, camptosar, CPT-11, leustatin, navelbine, rituxan, STI-571, taxotere, topotecan, hycamtin, xeloda capecitabine, zevelin, and combinations thereof.

70. A method for the treatment or prevention of a hypoxia-related pathology comprising:

administering to a host in need of such treatment an HIF-1 inhibiting amount of any of the compositions of claims 38-68.

71. A method of modulating HIF-1 activity in a cell comprising: contacting the cell with an HIF-1 inhibiting amount of any of the compositions of claims 38-68.

72. A method of treating or preventing cancer or a tumor in a host comprising administering to the host a HIF-1 inhibiting amount of any of the compositions of claims 38-68.

73. The method of claim 72, wherein the cancer or tumor is selected from the group consisting of bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head & neck cancer, leukemia, lung cancer, lymphoma, melanoma, non-small-cell lung cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, cervical cancer, thyroid cancer, gastric cancer, brain stem glioma, cerebellar astrocytoma, cerebral astrocytoma, ependymoma, Ewing's sarcoma family of tumors, germ cell tumor, extracranial cancer, Hodgkin's disease, leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, liver cancer, medulloblastoma, neuroblastoma, brain tumors generally, non-Hodgkin's lymphoma, osteosarcoma, malignant fibrous histiocytoma of bone, retinoblastoma, rhabdomyosarcoma, soft tissue sarcomas generally, supratentorial primitive neuroectodermal and pineal tumors, visual pathway and hypothalamic glioma, Wilms' tumor, acute lymphocytic leukemia, adult acute myeloid leukemia, adult non-Hodgkin's lymphoma, chronic lymphocytic leukemia, chronic myeloid leukemia, esophageal cancer, hairy cell leukemia, kidney cancer, multiple myeloma, oral cancer, pancreatic cancer, primary central nervous system lymphoma, skin cancer, and small-cell lung cancer.

74. A method of modulating gene transcription in a cell comprising contacting the cell with an HIF-1 inhibiting amount of one or more of the compositions of any of claims 38-68.

75. The method of claim 74, wherein the cell is a cancer cell.

76. The method of claim 74, wherein the gene is VEGF, erythropoietin, glucose transporter-1, glycolytic enzymes, or tyrosine hydroxylase.